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Intraocular use of methotrexate (MTX) for the treatment of proliferative vitreoretinopathy (PVR) in congenital aniridia (CI) and a possible link to aniridia fibrosis syndrome (AFS) treatment

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ABSTRACT

Purpose: To present a case of aggressive proliferative vitreoretinopathy (PVR) managed with intraoperative and postoperative intravitreal methotrexate (MTX) in a patient with congenital aniridia (CI).

Observations: A 41-year-old female with a history of CI, living-related conjunctival-kerato-limbal allograft transplantation, and multiple intraocular surgeries presents with tractional retinal detachment (TRD) and aggressive grade C PVR 52 days after a primary 23-gauge pars plana vitrectomy (PPV) with rhegmatogenous retinal detachment repair. She underwent 23-gauge PPV, TRD repair including membrane peeling of pre- and sub-retinal PVR, 5000 centistoke silicone oil exchange, endolaser, and MTX infusion. She received intravitreal 200 μg/0.05mL MTX every two weeks for a total of five injections before switching to monthly injections which have continued indefinitely. Five months after TRD repair, she had a small area of recurrent PVR inferiorly without associated retinal traction. She developed a small epithelial defect that resolved without complication. At 13 months, the patient remains at her visual acuity baseline of 20/125 and an attached retina without progression of PVR.

Conclusions and importance: We report a favorable outcome in the management of aggressive PVR with intraoperative and postoperative intravitreal MTX in a patient with CI. Despite a history of limbal stem cell deficiency and receiving numerous MTX injections, keratopathy was minimal. Further research is required to study the safety and efficacy of MTX in the prophylaxis and treatment of aggressive fibrotic responses often seen in CI.

1. Introduction

Proliferative vitreoretinopathy (PVR) is a devastating complication of rhegmatogenous retinal detachment (RRD).[1] PVR consists of fibrocellular proliferation within the vitreous, on the retina, within the retina, or under the retina. It most commonly occurs 30–60 days after RRD and is the most common reason for re-detachment after primary RRD repair.[2] Currently, the only established treatment is pars plana vitrectomy and removal of membranes. There is growing interest in using intravitreal methotrexate (MTX) to prevent and treat PVR. MTX decreases DNA replication by acting as a folate antagonist and has anti-proliferative, anti-inflammatory, and anti-fibrotic properties.[1,2] An increasing number of reports have suggested efficacy and safety of intravitreal MTX for PVR prevention although level one evidence is lacking.[1–17]

Congenital aniridia (CI) is a rare inherited (1:50,000 to 1:100,000) syndrome often associated with *PAX6* gene mutations with variable phenotypes including iris defects, secondary glaucoma, corneal epitheliopathy, cataract, nystagmus and foveal hypoplasia.[18] Approximately 5% of eyes with CI who undergo intraocular (typically anterior segment) surgery develop aniridia fibrosis syndrome (AFS) which is an obliterative fibro-cellular reaction thought to emanate from mechanical stimulation of the immature aniridic iris root.[19]

We report an excellent outcome of PVR treated with both intraoperative infusion and postoperative intravitreal injections of MTX in a patient with congenital aniridia.

2. Case presentation

A 41-year-old female with a history of congenital aniridia presented

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to the clinic for a macula involving RRD in her right eye. She had a past history of cataract surgery with capsular tension ring and iris prosthesis implantation combined with living-related conjunctival-kerato-limbal allograft transplantation four months prior. Her medication regimen included difluprednate six times daily, cyclosporine eye drops twice a day, brimonidine/timolol twice a day, an oral prednisone taper, mycophenolic acid, tacrolimus, and valganciclovir. Past medical and family history were noncontributory.

Visual acuity was 20/500; baseline vision prior to RD was 20/80. Examination revealed a loose artificial iris prosthesis - intraocular lens - capsular tension ring - capsular bag complex and a total retinal detachment with large 12:00 and 6:00 retinal breaks. Three days later, the patient underwent 23-gauge pars plana vitrectomy with rhegmatogenous retinal detachment repair consisting of complete peeling of the posterior hyaloid, perfluoro-n-octane placement, focal wall-off endolaser, air-fluid exchange, posterior drainage retinotomy, and placement of 5000 centistoke silicone oil. 40 mg of methotrexate was placed into the 500mL BSS posterior segment infusion bottle. Proliferative vitreoretinopathy was not observed preoperatively or intraoperatively. Postoperatively, the patient's difluprednate regimen was increased to every 2 h. Visual acuity at post operative week two was 20/100 and a difluprednate taper was initiated at this visit. No postoperative methotrexate injections were administered due to concern for corneal epitheliopathy in this congenital aniridia patient who had already received a keratolimbal allograft.

52 days postoperatively, vision worsened to counting fingers from a new progressive tractional retinal detachment (TRD) with aggressive grade C pre-and sub-retinal PVR under oil (Fig. 1). Eight days later, the patient underwent a 23-gauge pars plana vitrectomy, TRD repair including membrane peeling of pre- and sub-retinal PVR, 5000 centistoke silicone oil exchange, endolaser, and repeat MTX infusion. The patient resumed difluprednate drops every 2 h.

At post operative month one, vision was 20/125 (Fig. 2). She received intravitreal 200 μg/0.05mL methotrexate every two weeks for a total of five injections before switching to monthly injections which we have continued indefinitely. Five months after TRD repair, exam was notable for recurrence of a small area of PVR inferiorly without associated retinal traction. 13 months after TRD repair, retina remained attached without progression of PVR and visual acuity measuring 20/100 through oil (Fig. 3).

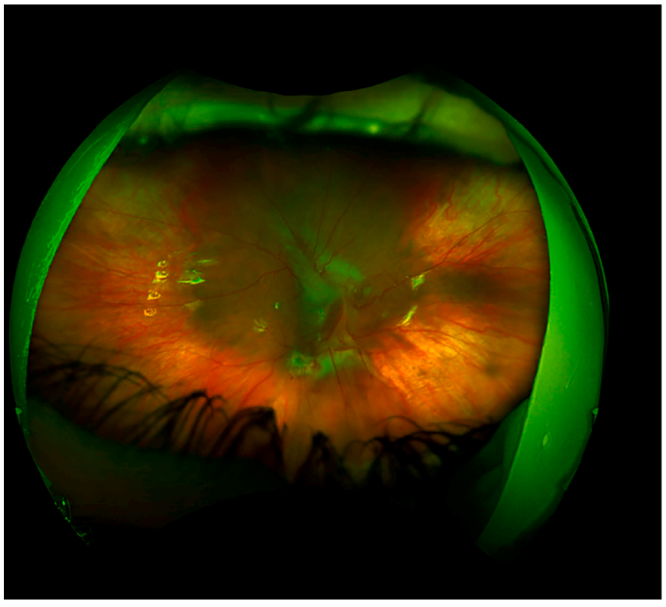

Fig. 1. Pre-operative Fundus Photo
Fundus photograph of the right eye showing Grade C pre-/sub-retinal proliferative vitreoretinopathy membranes involving the macula.

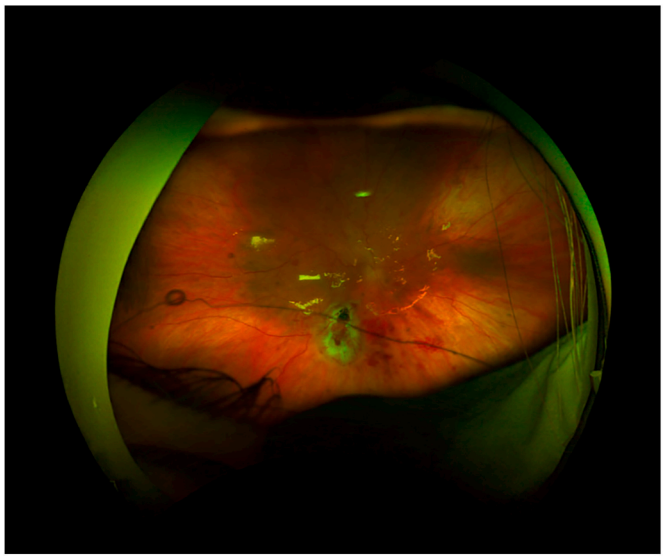

Fig. 2. Post-operative Month One Fundus Photo
Fundus photograph of the right eye at post-operative month one s/p tractional retinal detachment repair.

After eight monthly methotrexate injections, she developed mild corneal toxicity with 3+ punctate epithelial erosions and subsequently a small epithelial defect that resolved with artificial tears and pressure patching. Total length of follow up since her second surgery has been 20 months.

The patient was found to be heterozygous for the c.718C > T (p.Arg240*) variant in the *PAX6* gene using next-generation sequencing and confirmed with sanger sequencing from peripheral blood (Invitae, San Francisco, CA, USA, CAP/CLIA certified). This variant was classified as pathogenic and is associated with autosomal dominant aniridia.[20]

3. Discussion

We present a unique case of Grade C PVR managed with intraoperative and postoperative MTX in a patient with CI and RRD following complex anterior segment surgery. Despite extreme pre- and sub-retinal PVR membranes, the patient recovered and sustained her baseline visual acuity without retinal re-detachment and minimal corneal toxicity after frequent postoperative methotrexate dosing.

Aniridia fibrosis syndrome (AFS) is a condition that was first reported by our group in 2005.[19] We described seven eyes of six patients with congenital aniridia, all of whom had a history of numerous ocular surgeries with intraocular hardware who developed a progressive fibrotic reaction in the anterior chamber. Fibrosis appeared to originate from the primitive iris root and spread into the anterior chamber but has also been shown to spread posteriorly to affect the ciliary body and anterior retina. These six patients represented 8% of 80 CI patients and 5% of 155 CI eyes that had intraocular surgery (all with implanted hardware). Two additional cases of AFS occurred in a subsequent unpublished series of 50 CI (4%) eyes operated by another surgeon in our group.[21] We also published the only high-definition endoscopic images of posterior segment AFS in 2013.[22] There is no established etiology for AFS, but one hypothesis is that PAX6 gene mutations may contribute to improper regulation of fibrosis pathways representing a pro-fibrotic and pro-proliferative state.[23] Though our patient did have a history of multiple intraocular surgeries and intraocular hardware in addition to dislocation of the pseudo-iris – capsular tension ring – IOL and capsular bag complex, she did not have the classic presentation of AFS, but did have an atypical and overly exuberant fibrotic PVR reaction involving the posterior segment after a completely atraumatic and optimal RRD

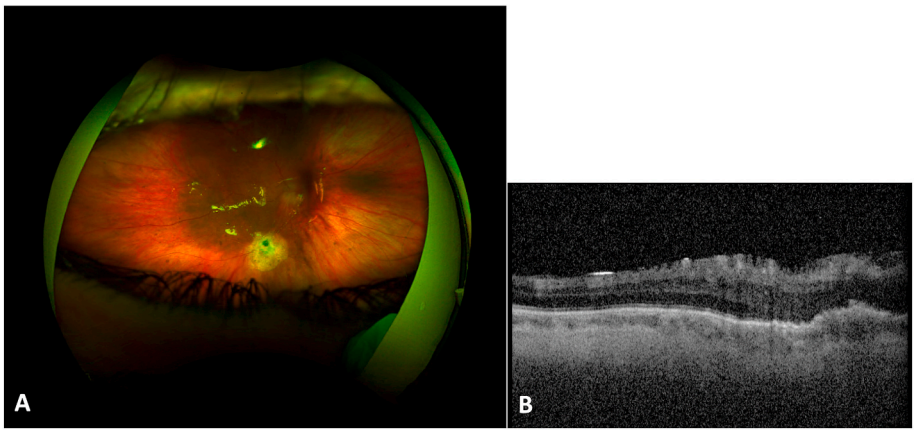

Fig. 3. Post-operative Month Ten Fundus and OCT Image
Postoperative month ten s/p tractional retinal detachment repair. (A) Fundus photograph of right eye. (B) Optical coherence tomography slice posterior to the posterior retinotomy demonstrating flat and attached macula with epiretinal membrane.

repair. The PAX6 gene mutation may have predisposed this patient to develop a posterior segment phenotype of AFS, which is a phenomenon we have seen previously in other CI patients with RD.

The use of MTX in the setting of PVR prevention was first reported by our group[3–6] and other groups have also published reports[7–10,12–15,24] suggesting potentially important anti-PVR efficacy of MTX in the setting of diseased eyes at elevated risk of PVR and eyes with recurrent PVR. Early data from the GUARD trial, a multi-center prospective randomized control trial demonstrated a statistically significant decrease in the rate of redetachment at month six in eyes with PVR that received intraoperative and postoperative MTX.[7] Our group is also conducting the FIXER Trial (FDA.gov #NCT06541574) which is currently recruiting patients to study MTX efficacy for PVR prevention in the setting of primary RRD repair.

While the development of PVR and need for reoperation despite initial intraoperative intraocular MTX infusion in our patient may suggest methotrexate inefficacy or failure, we suggest that the somewhat later presentation of PVR (52 days) supports a beneficial treatment effect of intraoperative intraocular MTX infusion. The development of PVR may be due to our reluctance to continue therapy with post-operative injections for fear of corneal toxicity complications. Whether post-operative injections of MTX after the first vitrectomy may have prevented the need for a second surgery is not known, but we strongly believe that the possibility should not be ignored.

During the second surgery, the patient was again treated with intraoperative intraocular MTX infusion and subsequently treated with frequent postoperative MTX injections. These have been well tolerated with only one episode of corneal epithelial defect that healed completely with conservative management and without stopping MTX injections.

This is a unique report describing intraocular MTX in the setting of CI, known aniridic keratopathy and the presence of a keratolimbal allograft. In this single case, the excellent safety profile of intense MTX therapy is worthy of note and calls for further research into the safety of MTX in patients with high risk of corneal toxicity. Subsequently, the use of MTX may be considered in carefully selected patients with CI or limbal stem cell deficiency.

Aniridia likely represents a pro-proliferative state. Our center has a great deal of experience with CI patients and can anecdotally report that RRD – thankfully rare in CI patients whose pathology is usually limited to the anterior segment – in CI is often accompanied by PVR complications and that the intersection of and differentiating features distinguishing PVR and AFS are often muddled and difficult to differentiate by clinical observation. While AFS is not PVR and PVR is not AFS, they certainly have clinical biomarkers in common including protean fibrocellular proliferation, contraction and obliteration of normal underlying neurosensory and uveal anatomy. Regardless, AFS in the CI patient after anterior segment surgery and AFS-PVR after retinal detachment repair in the CI patient both represent rare subsets of already rare orphan diseases. Notwithstanding the epidemiology of rare diseases and difficulty in studying them, a solution to AFS represents a pressing unmet need for CI patients who have a 5% risk of often catastrophic AFS complications after intraocular surgery which many CI patients will require at some point in their lives.[19]

Combining our experience with a large number of CI patients and using MTX for PVR prevention since 2006, we feel empowered to more aggressively explore treating CI patients with MTX going forward and suggest a study group be formed to investigate the utility of MTX for complication reduction in patients with CI undergoing intraocular surgery.

4. Conclusions

We report a favorable outcome in the management of aggressive Grade C PVR with intraoperative and postoperative intravitreal MTX in a patient with CI and a history of limbal stem cell deficiency.

CRediT authorship contribution statement

Naveen R. Ambati: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christopher D. Riemann:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Patient consent

Consent to publish this case report has been obtained from the patient(s) in writing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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